NITROSAMINES: CHALLENGES & RECOMMENDATIONS

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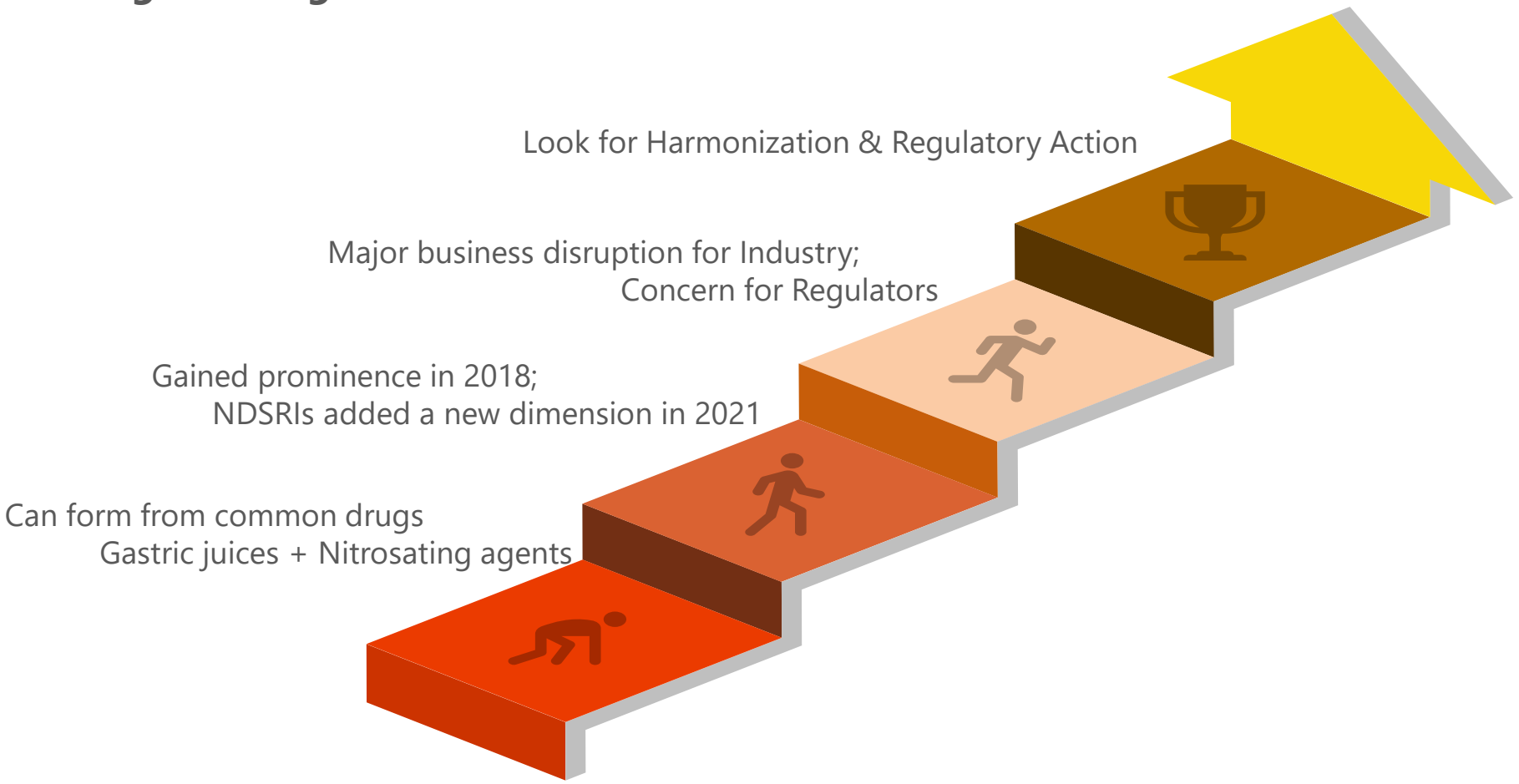
BRIEF

Long standing concern since 70's



Challenges

01 **Lack of Consensus**

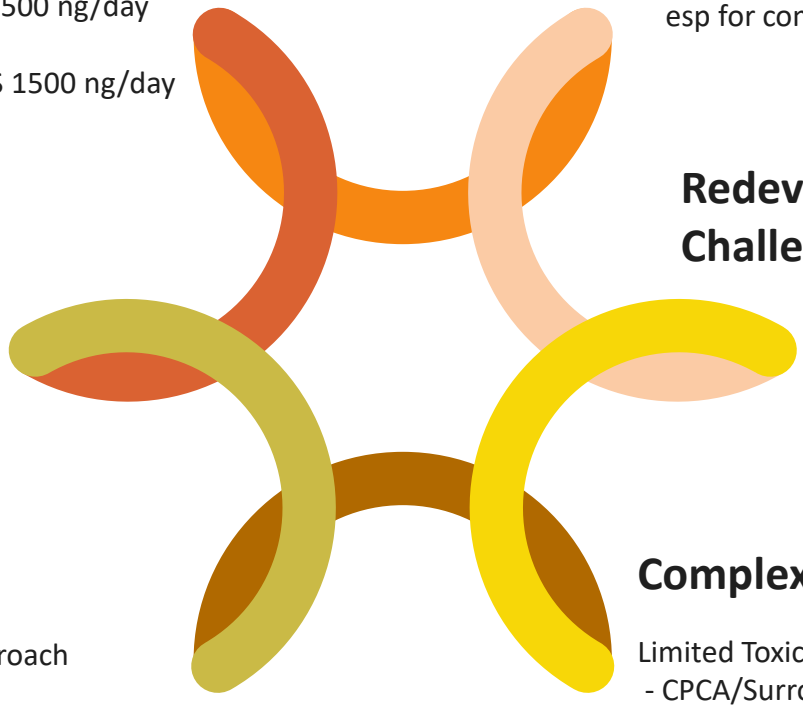
Same API Different Limits
Eg: N-nitroso-ciprofloxacin (US 1500 ng/day
EU: NMI)
N- nitroso Clarithromycin (US 1500 ng/day
EU: NMI)

02 **Deriving Limits**

Different Ways of proposing limits in EU/ US only recently adopted the flexible approach

03 **LTL Approach**

EU recommends LTL approach
Canada/US do not



04 **Supply Continuity**

Testing/Assessment/Workload
esp for companies with large SKUs

05 **Redevelopment Challenges**

Time/Resources/Cost
-Testing methods/ Equipment's

Regulatory Challenges

06 **Complex Risk Evaluations**

Limited Toxicity data particularly for NDSRIs
- CPCA/Surrogate/EAT based approach not working
Agencies are insisting on invivo-mutagenicity
Relevant surrogate : challenging

Recommendations For Regulators To Consider

1. Balanced Risk Benefit; learn from each other; Harmonize limits esp in case of impurities categorized as Non-Mutagenic.

2. Accept **Less than Lifetime (LTL)** approach: Well defined tenure

   - Does not lead to any disproportionate increase in the risk to patients
   - Allows Pharmaceutical Companies to maintain Supply continuity
   - Allows for time to develop cost effective processes that ensure that the products in market remain viable

3. Treat **metabolites** differently: minimal risk and can be evaluated as non 'Cohort of Concern'

4. Greater **Agency-Industry Collaboration;** share Toxicological findings on NDSRIs.

5. **Acceptance of theoretical Risk Assessments** backed by robust surrogate analogues and an appropriate SAR/CADRE review
   - High accuracy
   - In-vivo mutagenicity data is prohibitively costly and time consuming

6. Elaborate criteria for choosing **Surrogates**.

SURROGATES : SOME OPTIONS

- Similarity Assessment
  - Must compares all features in a molecule, not just those of greatest relevance to endpoint of concern
    - the degree of substitution
    - steric bulk
    - electronic influences
    - potential for metabolic activation*
    - stability/reactivity

    * For Nitrosamines, mutagenicity and carcinogenicity are more heavily dependent on immediate nitrosamine environment due to need for metabolic activation

  - Tanimoto coefficient/Dice coefficient can be used to establish similarity

- Recommendations in CPCA guidance

Deactivating Features		Activating Features
Substitution at α-carbon	Presence of carboxylic acid group	Unsaturated carbon-carbon bond at α-position
Nitrosamine in smaller than 6-membered ring	Electron withdrawing group in β-position	Methyl group directly bonded to one side of nitrosamine
Presence of hydroxyl groups	Increasing alkyl chain length	β-methyl group

- Surrogates with both CPDB and LCDB TD50

Industry's Dilemma

FDA's Deadline

Till August 2025------WHAT?

THANK YOU

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